Polycystic Ovarian Syndrome and Hyperandrogenism

- Common endocrinopathy typified by:
    - Oligoovulation or anovulation,
    - Signs of androgen excess, and
    - An excess of small ovarian cysts
- Also have higher rates of obesity, dyslipidemia, and insulin resistance
- PCOS currently is a diagnosis of exclusion
- Congenital adrenal hyperplasia, androgen-secreting tumors, and hyperprolactinemia,
    - Also may lead to oligo-ovulation and/or androgen excess, these must be excluded

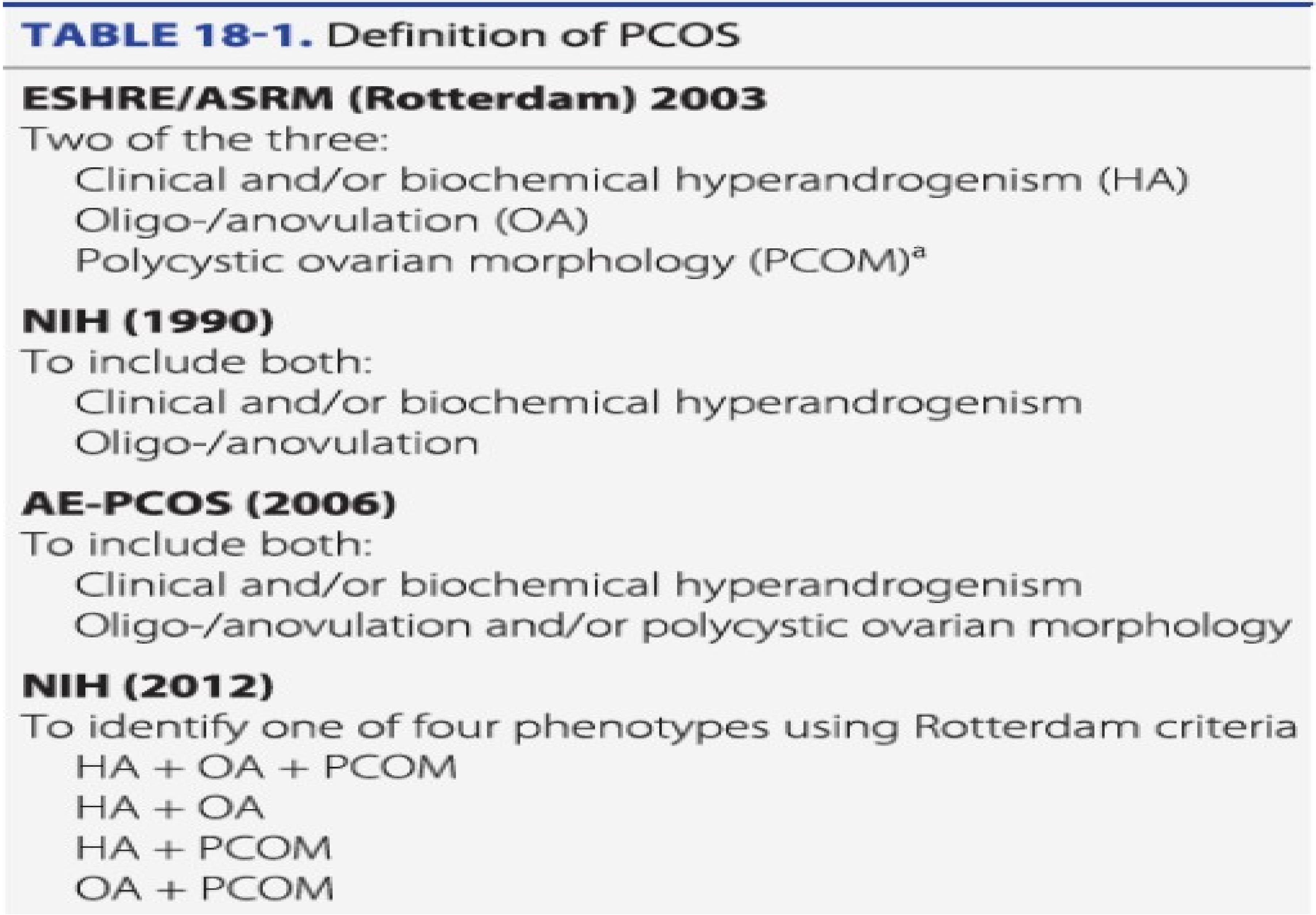


TABLE 18-1. Definition of PCOS

ESHRE/ASRM (Rotterdam) 2003

Two of the three:

- Clinical and/or biochemical hyperandrogenism (HA)
- Oligo-/anovulation (OA)
- Polycystic ovarian morphology (PCOM)[a]

NIH (1990)

To include both:

- Clinical and/or biochemical hyperandrogenism
- Oligo-/anovulation

AE-PCOS (2006)

To include both:

- Clinical and/or biochemical hyperandrogenism
- Oligo-/anovulation and/or polycystic ovarian morphology

NIH (2012)

To identify one of four phenotypes using Rotterdam criteria

- HA + OA + PCOM
- HA + OA
- HA + PCOM
- OA + PCOM

- ■ Ovarian Hyperthecosis and HAIRAN Syndrome

- **Ovarian hyperthecosis,**
  - often considered a more severe form of PCOS,
  - is a rare condition characterized by nests of luteinized theca cells distributed throughout the ovarian stroma.

- Hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome
  - also is uncommon and consists of marked hyperandrogenism, severe insulin resistance, and acanthosis nigricans

- INCIDENCE AND ETIOLOGY
  - Most common endocrine disorder of reproductive-aged women
  - Affects approximately 6 to 16 percent
  - Underlying cause of PCOS is unknown
  - Some have suggested an autosomal dominant inheritance with expression in both females and males

- PATHOPHYSIOLOGY
- Gonadotropins
  - Anovulation in women with PCOS is characterized by inappropriate gonadotropin secretion
    - Specifically, altered GnRH pulsatility leads to preferential production of LH compared with FSH
  - Elevated LH levels are observed clinically in approximately 50 percent of affected women
  - Similarly, LH:FSH ratios are elevated and rise above 2: 1 in approximately 60 percent of patients

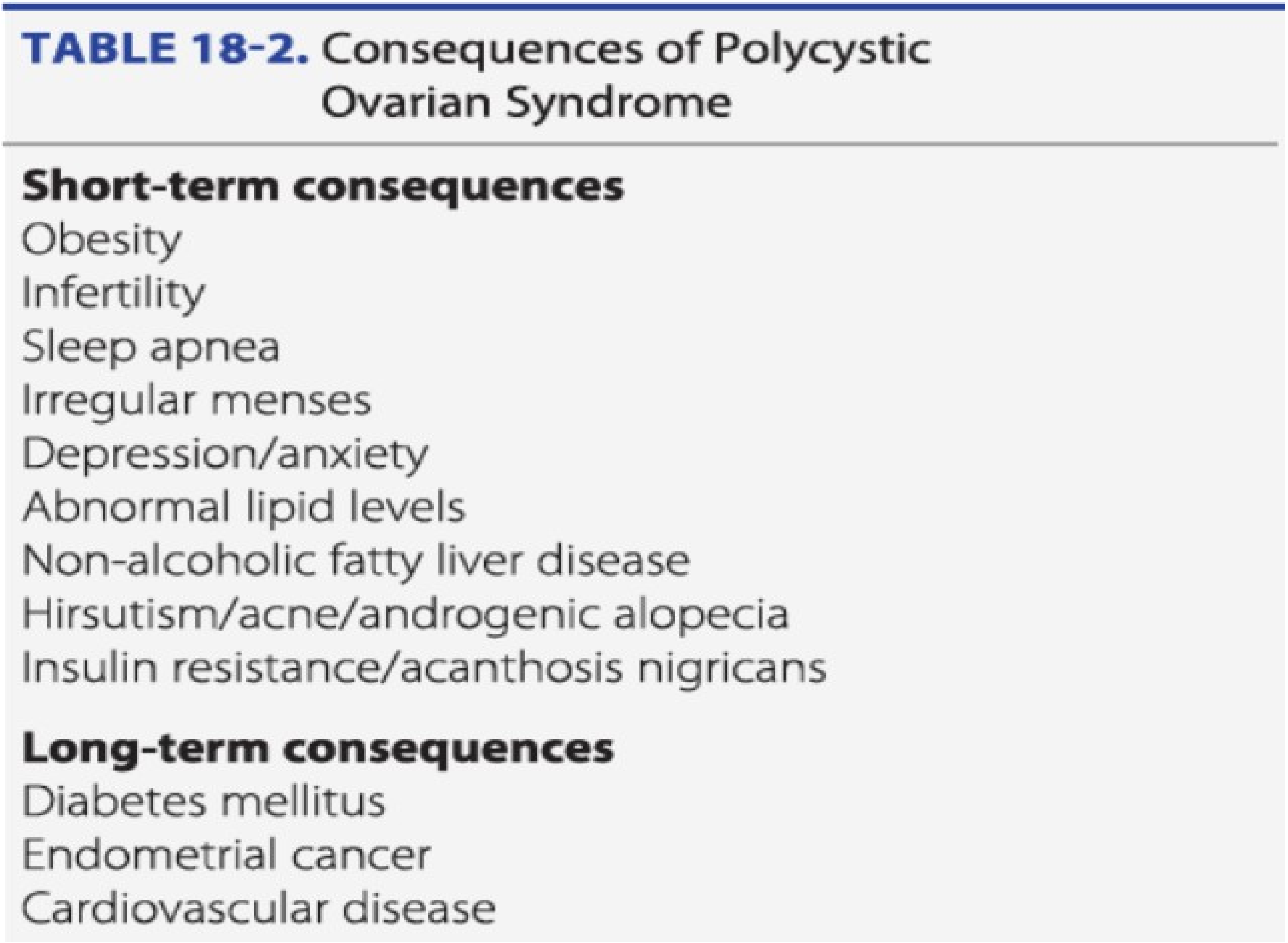


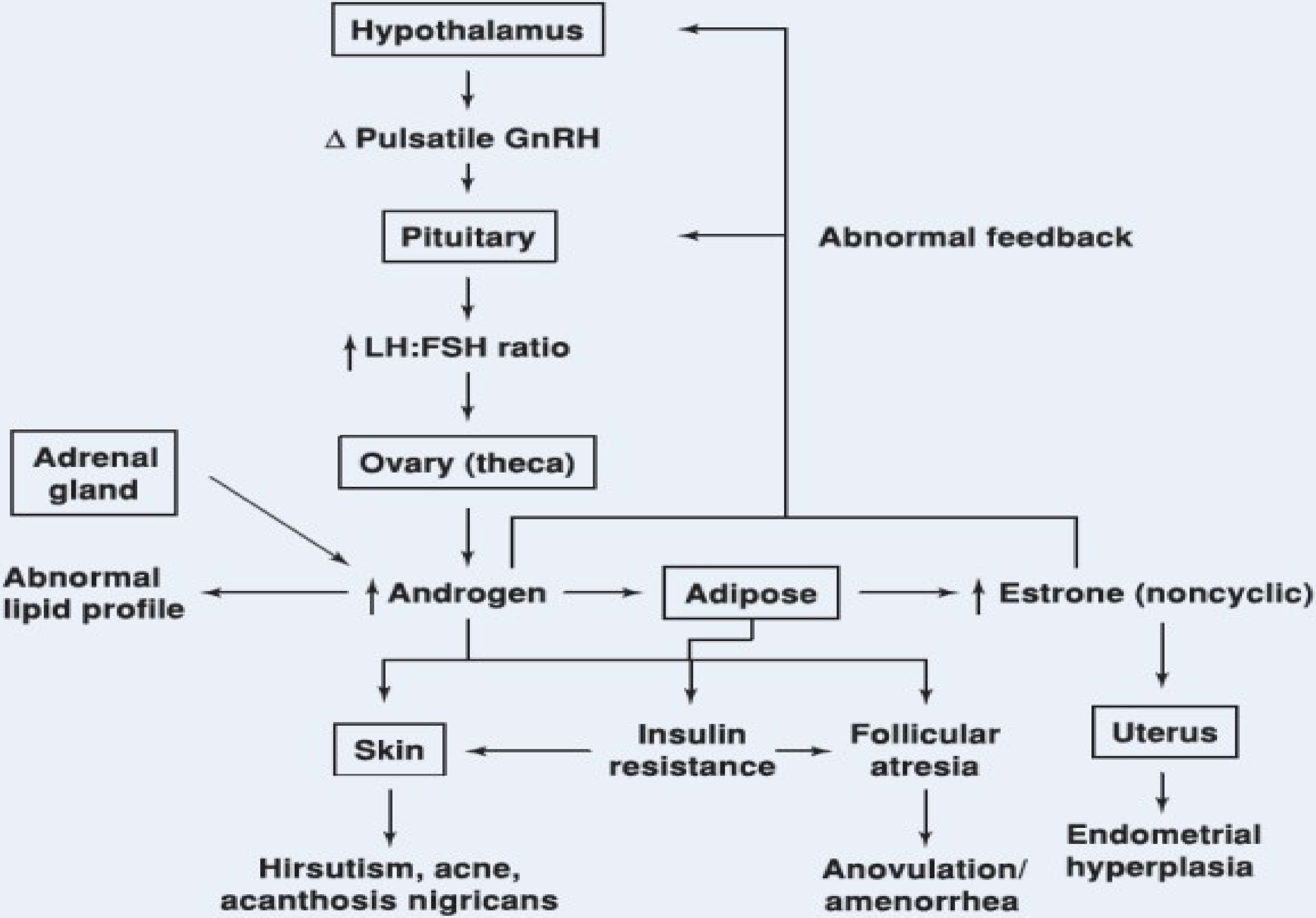
TABLE 18-2. Consequences of Polycystic Ovarian Syndrome

Short-term consequences
Obesity
Infertility
Sleep apnea
Irregular menses
Depression/anxiety
Abnormal lipid levels
Non-alcoholic fatty liver disease
Hirsutism/acne/androgenic alopecia
Insulin resistance/acanthosis nigricans
Long-term consequences
Diabetes mellitus
Endometrial cancer
Cardiovascular disease

- Insulin resistance
  - Display greater degrees of insulin resistance and compensatory hyperinsulinemia than nonaffected women
  - Insulin resistance is associated with several disorders including:
    - Type 2 diabetes mellitus (DM),
    - Hypertension,
    - Dyslipidemia, and
    - Cardiovascular disease (CVD)

- Androgens
  - Both insulin and LH stimulate androgen production by the ovarian theca cell
  - As a result, affected ovaries secrete elevated levels of testosterone and androstenedione (70 to 80%) and 25 to 65% exhibit elevated levels of DHEAS
  - elevated androstenedione levels contribute to greater estrone levels through peripheral conversion of androgens to estrogens by aromatase

- Sex Hormone-Binding Globulin
  - **Decrease in PCOS**
  - The synthesis of SHBG is suppressed by:
    - insulin and by androgens,
    - corticoids,
    - progestins, and
    - growth hormone
  - low SHBG levels also have been linked to impaired glucose control and a risk for developing type 2 DM



Hypothalamus

Δ Pulsatile GnRH

Pituitary

↑ LH:FSH ratio

Ovary (theca)

Abnormal feedback

Adrenal gland

↑ Androgen

Abnormal lipid profile

Adipose

↑ Estrone (noncyclic)

Skin

Insulin resistance

Follicular atresia

Uterus

Hirsutism, acne, acanthosis nigricans

Anovulation/ amenorrhea

Endometrial hyperplasia

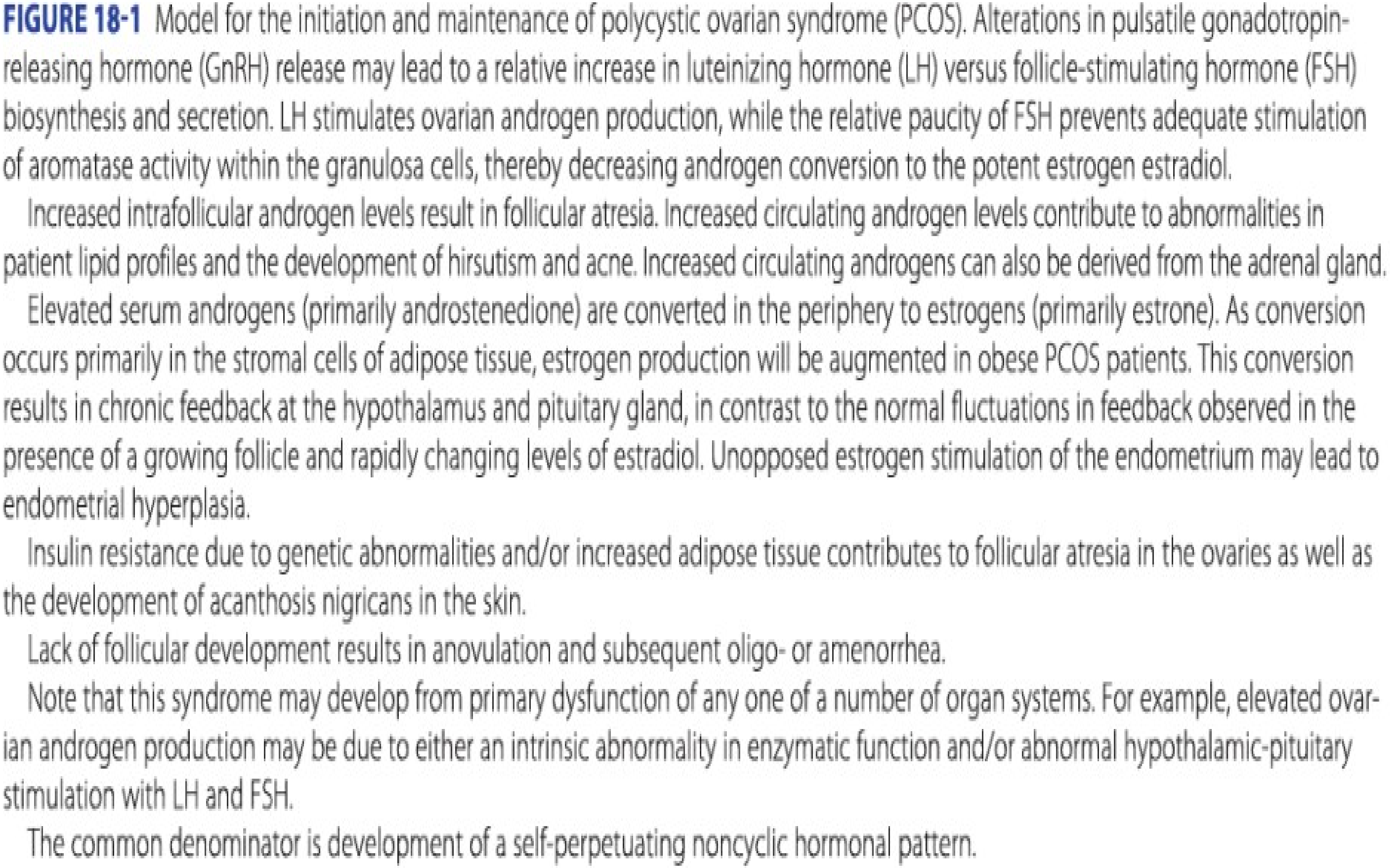


FIGURE 18-1 Model for the initiation and maintenance of polycystic ovarian syndrome (PCOS). Alterations in pulsatile gonadotropin-releasing hormone (GnRH) release may lead to a relative increase in luteinizing hormone (LH) versus follicle-stimulating hormone (FSH) biosynthesis and secretion. LH stimulates ovarian androgen production, while the relative paucity of FSH prevents adequate stimulation of aromatase activity within the granulosa cells, thereby decreasing androgen conversion to the potent estrogen estradiol.

Increased intrafollicular androgen levels result in follicular atresia. Increased circulating androgen levels contribute to abnormalities in patient lipid profiles and the development of hirsutism and acne. Increased circulating androgens can also be derived from the adrenal gland.

Elevated serum androgens (primarily androstenedione) are converted in the periphery to estrogens (primarily estrone). As conversion occurs primarily in the stromal cells of adipose tissue, estrogen production will be augmented in obese PCOS patients. This conversion results in chronic feedback at the hypothalamus and pituitary gland, in contrast to the normal fluctuations in feedback observed in the presence of a growing follicle and rapidly changing levels of estradiol. Unopposed estrogen stimulation of the endometrium may lead to endometrial hyperplasia.

Insulin resistance due to genetic abnormalities and/or increased adipose tissue contributes to follicular atresia in the ovaries as well as the development of acanthosis nigricans in the skin.

Lack of follicular development results in anovulation and subsequent oligo- or amenorrhea.

Note that this syndrome may develop from primary dysfunction of any one of a number of organ systems. For example, elevated ovarian androgen production may be due to either an intrinsic abnormality in enzymatic function and/or abnormal hypothalamic-pituitary stimulation with LH and FSH.

The common denominator is development of a self-perpetuating noncyclic hormonal pattern.

- Anovulation
  - May be due to altered GnRH pulsatility
  - may result from insulin resistance
  - the large antral follicle colon and associated higher intraovarian androgen levels

- SIGNS AND SYMPTOMS
  - menstrual irregularities, infertility, manifestations of androgen excess, or other endocrine dysfunction
  - become apparent within a few years of puberty
- ■ Menstrual Dysfunction
  - range from amenorrhea to oligomenorrhea to episodic heavy menstrual bleeding with associated iron-deficiency anemia
  - chronic estrogen exposure□ leads to unpredictable bleeding.
  - Oligomenorrhea (fewer than nine menstrual periods in 1 year) or amenorrhea (absence of menses for 3 or more consecutive months) with PCOS usually begins with menarche
  - fail to establish monthly ovulatory menstrual cycles

- Menstrual intervals 45 days in girls 2:2 years after menarche or menstrual interval >90 days any time after menarche merits consideration of further evaluation
- As women with PCOS age, those with prior irregular cycle intervals may develop regular cycle patterns
- Amenorrhea can stem from elevated androgen levels
  - androgens can counteract estrogen to produce an atrophic endometrium

- HYPERANDROGENISM
  - manifested clinically by hirsutism, acne, and/or androgenic alopecia
  - In contrast, signs of virilization such as increased muscle mass, voice deepening, and clitoromegaly are not typical of PCOS
- 1. Hirsutism
  - is defined as coarse, dark, terminal hairs distributed in a male pattern
    - distinguished from hypetrichosis, which is a generalized increase in lanugo, that is, the soft, lightly pigmented hair associated with some medications and malignancies.
  - PCOS accounts for 70 to 80% of cases of hirsutism
  - Idiopathic hirsutism is the second most frequent cause

TABLE 18-3. Medications That May Cause Hirsutism and/or Hypertrichosis

Hirsutism	Hypertrichosis
Anabolic steroids	Cyclosporine
Danazol	Diazoxide
Metoclopramide	Hydrocortisone
Methyldopa	Minoxidil
Phenothiazines	Penicillamine
Progestins	Phenytoin
Reserpine	Psoralens
Testosterone	Streptomycin

- Pathophysiology of Hirsutism
  - Within a hair follicle, testosterone is converted by the enzyme 5a-reduccase to dihydrotescoscerone (DHT)
  - Although both testosterone and DHT convert short, soft vellus hair co coarse terminal hair, DHT is markedly more effective than testosterone
    - include the upper lip, chin, sideburns, chest, and linea alba of the lower abdomen
- Ferriman-Gallwey Scoring System
  - To quantify the degree of hirsutism for research purposes
  - abnormal hair distribution is assessed in nine body areas and scored from 0 to 4
  - Many investigators define hirsutism as a score ~4 to 6 using the modified scoring

- 2. Acne
  - acne that is persistent, moderate to severe, or late onset raises concern for PCOS or other androgen excess source
  - Prevalence is unknown
  - androgen level elevation has been reported in 80 percent of women with severe acne, 50 percent with moderate acne, and 33 percent with mild acne
  - Women with moderate to severe acne have an increased prevalence (52 to 83 percent) of polycystic ovaries
  - The pathogenesis of acne vulgaris involves four factors:
    - blockage of the follicular opening by hyperkeratosis,
    - sebum overproduction,
    - proliferation of commensal Propionibacterium acnes, and
    - inflammation

- As in the hair follicle, testosterone is converted within sebaceous glands to its more active metabolite, DHT, by 5a-reductase.
- In women with androgen excess,
  - overstimulation of androgen receptors in the pilosebaceous unit elevates sebum production that eventually leads to:
    - inflammation and comedone formation
- Inflammation leads to the main long-term side effect of acne-scarring.
- Accordingly, treatment is directed at:
  - minimizing inflammation,
  - decreasing keratin production,
  - lowering colonization of Propionibacterium acnes, and
  - reducing androgen levels to diminish sebum production

- 3. Alopecia
  - Female androgenic alopecia is a less common finding in women with PCOS.
  - Hair slowly thins diffusely at the crown, but the frontal hairline is preserved
  - three-grade Ludwig visual score is a recommended (Teede, 2019).
    - The perceptible thinning of grade I progressively worsens to total balding of the crown in grade III
  - Alopecia pathogenesis involves an excess of 5a-reductase activity in the hair follicle leading to a rise in DHT levels.

- ■ Other Endocrine Dysfunction
- Insulin Resistance
- Acanthosis Nigricans
  - thick, graybrown velvety plaques develop in flexure areas such as the back of the neck, axillae, inframammary creases, waist, and groin
    - Insulin resistance leads to hyperinsulinemia, which is believed to stimulate keratinocyte and dermal fibroblast growth, producing the characteristic skin changes
  - Optimal treatment for acanthosis nigricans is directed toward decreasing insulin resistance and hyperinsulinemia.
    - Topical retinoids are a first-line adjunct option
- Impaired Glucose Tolerance and Type 2 Diabetes Mellitus.

- Dyslipidemia
  - increased low-density lipoprotein (LDL) and triglyceride levels, elevated total cholesterol:high-density lipoprotein (HDL) ratios, but depressed HDL levels
  - ~ 70 percent
- Obesity
- Obstructive Sleep Apne
  - related to central obesity
  - 35 percent had
- Metabolic Syndrome and Cardiovascular Disease
  - characterized by insulin resistance, obesity, atherogenic dyslipidemia, and hypertension
- Endometrial Neoplasia
  - Risk increased three- to fourfold

- Infertility
- Complications in Pregnancy
  - who become pregnant experience a higher rate (30 to 50%) of early miscarriage
  - **Etiology is unknown but** Obesity is implicated
  - a metaanalysis of 17 studies failed to show an effect of metformin administration on miscarriage risk in women with PCOS
  - Of other pregnancy complications, higher risks of GDM, PIH and PTB have been noted
- Psychologic Health
  - anxiety, depression, eating disorders, and negative body image
  - screening for depression and anxiety is recommended

- DIAGNOSIS
  - Other potentially serious disorders may clinically appear similar to PCOS and are excluded during patient evaluation
- Thyroid-Stimulating Hormone and Prolactin
  - Elevated prolactin levels lead to anovulation through inhibition of GnRH pulsatile secretion
- Testosterone and Dehydroepiandrosterone Sulfate
  - Tumors of the ovary or adrenal are a rare but serious cause of androgen excess
  - total testosterone levels remain the best approach for identifying a possible tumor
  - Threshold values > 200 ng/ dL of total testosterone warrant evaluation for an ovarian lesion
  - serum DHEAS levels > 700 μg/dL are highly suggestive of an adrenal neoplasm

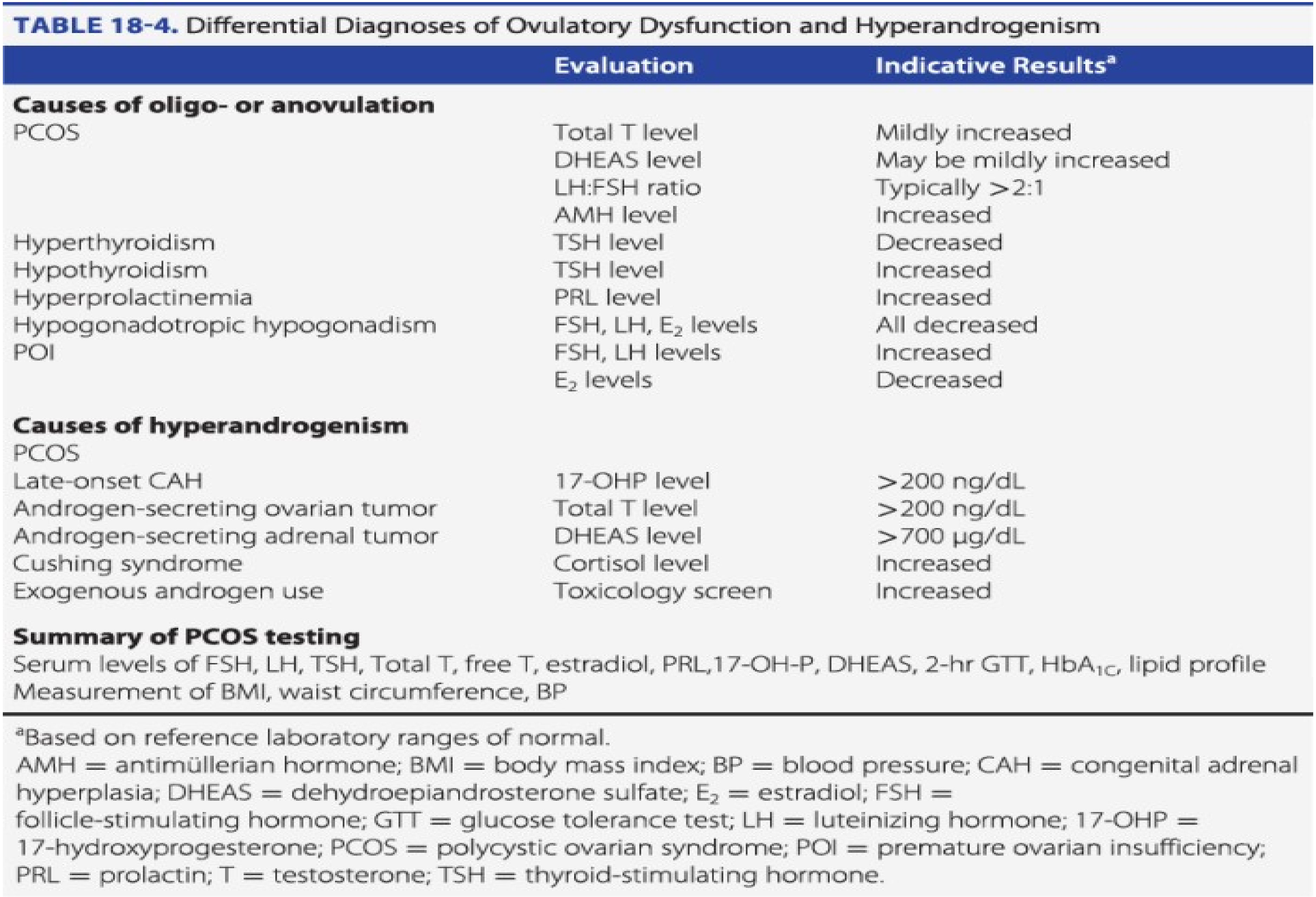


TABLE 18-4. Differential Diagnoses of Ovulatory Dysfunction and Hyperandrogenism

	Evaluation	Indicative Results[a]
Causes of oligo- or anovulation		
PCOS	Total T level	Mildly increased
	DHEAS level	May be mildly increased
	LH:FSH ratio	Typically >2:1
	AMH level	Increased
Hyperthyroidism	TSH level	Decreased
Hypothyroidism	TSH level	Increased
Hyperprolactinemia	PRL level	Increased
Hypogonadotropic hypogonadism	FSH, LH, E_2 levels	All decreased
POI	FSH, LH levels	Increased
	E_2 levels	Decreased
Causes of hyperandrogenism		
PCOS		
Late-onset CAH	17-OHP level	>200 ng/dL
Androgen-secreting ovarian tumor	Total T level	>200 ng/dL
Androgen-secreting adrenal tumor	DHEAS level	>700 µg/dL
Cushing syndrome	Cortisol level	Increased
Exogenous androgen use	Toxicology screen	Increased

Summary of PCOS testing

Serum levels of FSH, LH, TSH, Total T, free T, estradiol, PRL,17-OH-P, DHEAS, 2-hr GTT, HbA_{1C}, lipid profile

Measurement of BMI, waist circumference, BP

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[a] Based on reference laboratory ranges of normal.

AMH = antimüllerian hormone; BMI = body mass index; BP = blood pressure; CAH = congenital adrenal hyperplasia; DHEAS = dehydroepiandrosterone sulfate; E_2 = estradiol; FSH = follicle-stimulating hormone; GTT = glucose tolerance test; LH = luteinizing hormone; 17-OHP = 17-hydroxyprogesterone; PCOS = polycystic ovarian syndrome; POI = premature ovarian insufficiency; PRL = prolactin; T = testosterone; TSH = thyroid-stimulating hormone.

- ■ Gonadotropins
  - Although classicaJly LH levels measure at least twofold higher than FSH levels, this is not found in all women with PCOS
  - Specifically, one third of women with PCOS have circulating LH levels in the normal range, a finding more common in obese patients
  - Moreover, serum LH levels are affected by sample timing within a menstrual cycle, use of oral contraceptive pills, and BMI

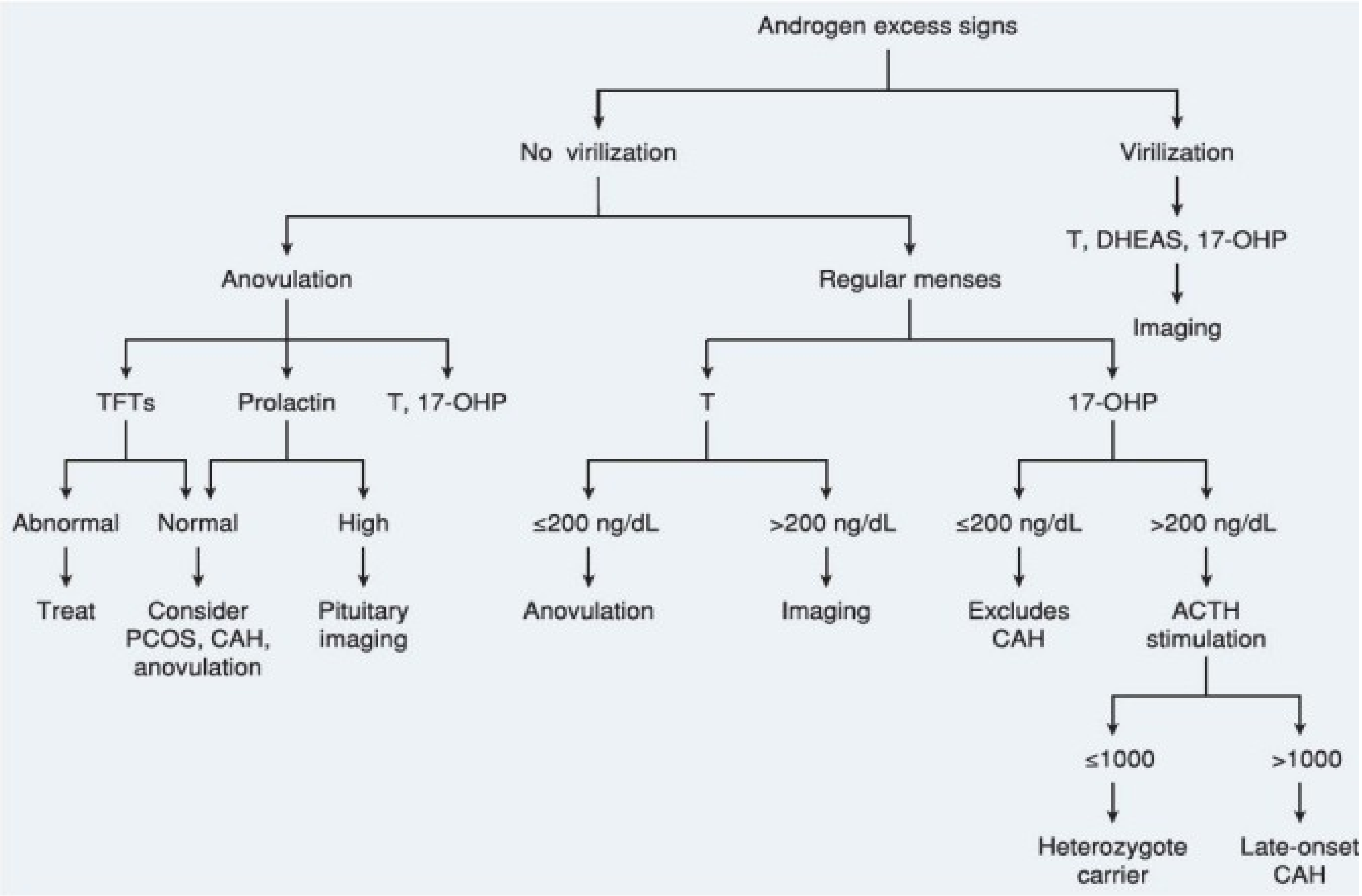

FIGURE 18-8 Algorithm for evaluation of androgen excess. 17-OHP = 17-hydroxyprogesterone; ACTH = adrenocorticotropin hormone; CAH = congenital adrenal hyperplasia; DHEAS = dehydroepiandrosterone sulfate; PCOS = polycystic ovarian syndrome; T = testosterone; TFTs = thyroid function tests.

- ■ 17-Alpha Hydroxyprogesterone
  - congenital adrenal hyperplasia (CAH) describes several autosomal recessive disorders that result from:
    - complete or partial deficiency of an enzyme involved in cortisol and aldosterone synthesis, usually 21-hydroxylase or less frequently 11-hydroxylase
  - Thus, depending on the enzyme affected, CAH symptoms vary.
  - It may present in the neonate with ambiguous genitalia and life-threatening hypotension

- late-onset form of CAH,
  - the enzyme deficiency leads to a relative cortisol deficiency.
  - In response, ACTH levels rise to normalize cortisol production
- Consequent to this accommodation, adrenal gland hyperplasia and elevated androgen levels develop
- With late-onset CAH, the most commonly affected enzyme is 21-hydroxylase, and deficiency leads to accumulation of its substrate, 17-hydroxyprogesterone

- Threshold values of 17-hydroxyprogesterone that measure > 200 ng/ dL should prompt an ACTH stimulation test.
- With this test, synthetic ACTH, 250 µg, is injected intravenously, and a serum 17-hydroxyprogesterone level is measured 1 hour later.
- Levels > I 000 ng/dL from blood drawn after synthetic ACTH is given are indicative of late-onset CAH

- ■ Antimullerian Hormone
  - The classic polycystic ovary contains two- to threefold more growing preantral and antral follicles than normal ovaries
  - Within the granulosa cells of these developing follicles, the dimeric glycoprotein antimullerian hormone (AMH) is produced.
  - Serum AMH levels correlate closely with the number of preantral and antral follicles
  - AMH levels are two- to threefold higher

- Cortisol
  - Cushing syndrome
  - Of these, a 24-hour urine collection for urinary free cortisol excretion can be obtained.
  - Alternatively, a dexamethasone suppression test administers I mg of dexamethasone orally at 11 PM, and a plasma cortisol level is measured at 8 AM the following morning.

- Sonography
  - Histologically, a polycystic ovary displays a greater number of ripening and atretic follicles, cortical stromal thickness, and number of hilar cell nests
  - Earlier sonographic criteria for PCOM included .:: 12 small cysts (2 to 9 mm in diameter) or an increased ovarian volume (>IO ml) or both per ovary
  - More recently, follicle number per ovary (FNPO) threshold values have been raised due to improved sonographic imaging resolution
    - threshold of>20 follicles and/or ovarian volume> 10 mL in either ovary has been adopted by ESHRE and ASRM
    - AE-PCOS guidelines use the same ovarian volume value but a higher FNPO threshold of .::25 follicles

- TREATMENT
- ■ Conservative Treatment
  - Women with PCOS who have fairly regular cycle intervals (8 to 12 menses per year) and mild hyperandrogenism may choose not to be treated
- ■ Treatment of Oligo- and Anovulation
- Hormonal Agents
  - COCs 1st line
    - induce regular menstrual cycles, lower androgen levels, and thin the endometrium
    - s suppress gonadotropin release, which results in decreased ovarian androgen production
    - estrogen component raises levels of SHBG□binds free androgen
    - **Progestin component decrese endometrial hyperplasia**

- Insulin Sensitizers
  - Metformin
    - help restore cyclic menses, lower hyperandrogenism, and aid weight loss
    - reserved for patients with PCOS and with IGT, elevated fasting insulin levels, and acanthosis nigricans

- ■ Hirsutism
  - a primary goal is lowering androgen levels to halt further conversion of vellus hairs to terminal ones
  - COCs
  - Hair Removal
  - Eflornithine hydrochloride
  - Spironolactone
  - Finasteride

- ■ Acne
- COC pills or spironolactone
- Topical benzoyl peroxide
- Topical retinoids
- Topical antibiotics
- Oral isotretinoin